

Obesity may shut down circadian clock in the cardiovascular system

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Obese individuals typically suffer more medical problems than their leaner counterparts. They are more likely to be diagnosed with insulin resistance, diabetes, increased stress hormones, hypothyroidism, and sleep apnea. Researchers at the Georgia Health Sciences University in Augusta have also found the potential for something else, using an animal model. They have found that a master clock gene – which regulates the cardiovascular system – does not fluctuate regularly as it does in non-obese animals. This means that a key gene clock of the cardiovascular system does not work properly when obesity is present. The findings are believed to be the first of their kind.

The study was conducted by Shuiqing Qiu, Eric Belin de Chantemele, James Mintz, David J. Fulton, R. Daniel Rudic and David W. Stepp. Members of the team will present their findings, entitled, "Impact of obesity on the vascular circadian clock," at the Experimental Biology 2011 meeting (EB 2011), being held April 9-13, 2011 at the Walter E. Washington Convention Center, Washington, DC.

Circadian Biology and Obesity

Humans and animals are essentially programmed to physiologically respond to a day/night cycles based on the 24-hour rotation of the planet. The body has been trained through evolution to respond to day cues by eating and perusing activities and to rest and sleep cues during darkness. Indeed, there is a molecular basis that precisely controls rhythms, a

group of genes dubbed the circadian clock, including one molecule also aptly named 'Clock'.

In [obese individuals](#), the natural circadian rhythms are believed to be disrupted. Obese individuals frequently eat at irregular times, and especially late at night. In addition, they often suffer from sleep apnea, which disturbs their sleep rhythm thus causing them to miss a good night's sleep. Shift workers tend to be obese because their physiological requirements are backwards (breakfast may start at 10:00 p.m.) and swing shift workers (who work a week on the day shift followed by a week on the night shift) are predisposed to obesity because their physiological cues "swing" back and forth thus interrupting the natural circadian rhythms.

The Study

With obesity known to affect at least the eat/[sleep](#) cycles, the researchers set out to determine whether obesity might also affect the molecular components of the clock that governs the vascular system, the system of the heart and blood vessels that are responsible for moving blood throughout the body. They conducted their research in two phases.

Methodology/Findings: I

In phase I, they examined the circadian variation in the cardiovascular chamber of three groups of mice (lean, obese and diabetic) at three time intervals: early morning, mid-day and evening, and measured the gene expression in the cardiovascular genes during these times.

In the lean animals they found evidence of a cardiovascular rhythm. Among the evidence was the presence of endothelial nitric oxide synthase (eNOS), an enzyme helps coordinate blood flow, thus tends to

be elevated at the end of the day and lower in the morning.

By contrast, they found this rhythm was lost in obese animals. For example, eNOS had either shifted its pattern, peaked at the wrong time, or was flat overall. The obese animals had thus lost their ability to control circadian variation of eNOS.

Methodology/Findings: II

In phase II, the team used the data to examine whether the lack of rhythmic response could translate into a cardiovascular defect. They did so by examining a series of specific molecules from the cardiovascular clock genes and by measuring the acceleration of the genes in the blood vessels.

In the lean animals they found that a key regulator of circadian rhythm, a gene called Clock, was high at 7:00 a.m. and low at 7:00 p.m. In the obese animals the expression of the gene remained flat throughout the 24-hour cycle.

Conclusions and Next Steps

David Stepp, Ph.D., a senior researcher on the team, summed up the findings by saying, "Based on the results of this study we now know that obesity impairs the clock machinery of the vasculature system and that correlates with a variation in expression of cardiovascular genes and their loss of the circadian rhythm." Having identified that the Clock gene does not work in the presence of obesity, he says the team has new studies underway to help explain why.

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